In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

ALEXI STOEV,	*	
	*	No. 19-1433V
Petitioner,	*	Special Master Christian J. Moran
	*	
v.	*	
	*	Filed: October 12, 2023
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Brian L. Cinelli, Schiffmacher Cinelli Adoff LLP, Buffalo, NY, for petitioner; Lynn Christina Schlie, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING ENTITLEMENT[1]

Alexi Stoev alleges that a human papilloma virus ("HPV") vaccine caused his complex regional pain syndrome ("CRPS") to worsen. The Secretary disputes this claim. The parties have developed evidence on this topic, including expert opinions, affidavits, and medical literature. The parties also submitted briefs. Mr. Stoev has not persuasively shown how an HPV vaccination can cause CRPS to worsen, or that his CRPS was aggravated by the vaccine. Accordingly, Mr. Stoev is not entitled to compensation.

[1] Because this Decision contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). This means the Decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), the parties have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. Any changes will appear in the document posted on the website.

I. Facts

A. Health Prior to Vaccination

Alexi Stoev was born in April 2001. Exhibit 1 (affidavit of Alexi Stoev) at 2. Mr. Stoev's parents are Steven Stoev and Muriel Stoev, who are both doctors. See Exhibits 2 and 3 (affidavits of Muriel and Steven Stoev). Mr. Stoev enjoyed various extracurricular activities, hobbies, and sports such as taekwondo and swimming. Exhibit 2 (affidavit of Muriel Stoev) at 2. On March 13, 2015, about month before he turned 14, Mr. Stoev was tripped by a classmate at a park. Exhibit 1 at 2. Approximately four days later, he began to experience severe leg pain. Id. The next day, he began to have difficulty walking and was tripping in school. Id. He ultimately had to use a wheelchair. Id.

Mr. Stoev underwent lab testing on March 19, 2015. Exhibit 29. He had a low c-reactive protein level (CRP) and a normal sed rate (also called erythrocyte sedimentation rate, or ESR), and his complete blood cell (CBC) and complete metabolic panel (CMP) results were both normal. Id.; see also Exhibit 5 at 6. His creatine kinase levels were elevated, but normalized within 5 days. Id.

On March 25, 2015, Dr. Muriel Stoev referred Mr. Stoev to Choice Diagnostic Imagine for an MRI of his femurs and lower legs. Exhibit 28. These were reviewed by rheumatologist Dr. Robert Nickeson at Johns Hopkins All Children's Hospital, who stated that they were unremarkable except for a small effusion in the right knee and showed no evidence for inflammatory myositis. Exhibit 5 at 6. Two days later, Mr. Stoev visited Dr. Gennady Gekht at Coastal Orthopedics for moderate-severe, constant, fluctuating bilateral leg pain. The pain was described as aching, burning, sharp, and throbbing. Exhibit 4 at 15. Mr. Stoev was assessed as likely having acute benign myositis, and was prescribed Neurontin, Klonopin, and Nucynta. Id. at 17. That same day, Mr. Stoev visited Dr. Nickeson. Exhibit 5 at 6. His chief complaint was leg pain beginning in March, especially in both calves. Id. Dr. Nickeson noted that Mr. Stoev also had some quad pain, but no joint symptoms.

Mr. Stoev went back to Dr. Gekht on March 30, 2015, presenting for bilateral leg pain. Exhibit 4 at 21. His pain was reported as severe, constant, and worsening. Mr. Stoev was ordered to increase Gabapentin and Baclofen, discontinue Nucynta, and prescribed Oxycontin and Hydromorphone. Id. at 23. Mr. Stoev went to a follow-up appointment on April 2, 2015. The doctor noted that the pain had spread, and Mr. Stoev had also developed left forearm burning. Id. at 26-28. The Oxycontin was discontinued. Id. at 29.

Mr. Stoev returned to Dr. Nickeson the next day. Exhibit 5 at 27. Dr. Nickeson noted red discoloration and tenderness on the left forearm, which resolved overnight. He also noted allodynia bilaterally from the thigh to the feet. Id. The joint exam was unremarkable. Dr. Nickeson observed that Mr. Stoev was showing features consistent with complex regional pain syndrome, but that the "[p]recipitating event history is questionable," as they had not identified any "definite trauma." Id. at 27-28. Dr. Nickeson recommended "aggressive physical therapy." Id. at 28.

Mr. Stoev visited Lakewood Ranch for an initial physical therapy evaluation on April 9, 2015. Exhibit 6 at 146. The impression was bilateral lower extremity reflex sympathetic dystrophy (another name for CRPS). Mr. Stoev was described as "an excellent candidate for restorative physical therapy" with a good prognosis. He began attending physical therapy 2-4 times per week.

Mr. Stoev went to Dr. Nickeson again on April 17, 2015, with a rash and pain on his chest and abdomen, distal to the elbows, and pain in both legs. Exhibit 5 at 54. The assessment was CRPS with continued moderately high symptoms. Id. at 55. Dr. Nickeson recommended that Mr. Stoev continue with aggressive physical therapy.

On June 8, 2015, Mr. Stoev was seen by Dr. David Sherry at The Children's Hospital of Philadelphia. Exhibit 8 at 1. The records note that Mr. Stoev developed leg pain without prior trauma, and that the pain began four days after he had been tripped. Id. at 4. "This has not been associated with autonomic changes. He has allodynia." Id. Mr. Stoev reported a 4.5/10 pain, going as high as 10/10 and as low as 3.5/10. The pain was made worse by activity, touching, time of day, stress, vibration, bathing, and cold. He also reported paralysis of his right hand and muscle spasms. Mr. Stoev was using a cane, walker, and/or wheelchair at this time.

Dr. Sherry's impression was diffuse amplified musculoskeletal pain with allodynia to the face, arms, upper back, and legs. Exhibit 8 at 7. Dr. Sherry recommended "intense physical and occupational therapy and desensitization (6 hours a day for an average of 3 weeks)," and noted that medications would not help. Dr. Sherry stated that Mr. Stoev's Functional Disability Index score was 34, which is in the severely disabled range. Dr. Sherry stated: "This condition is amendable to PT/OT but the quantity and quality of therapy is not available in Florida [where Mr. Stoev resides], therefore [Mr. Stoev] will need to come [to Philadelphia] for treatment. Without treatment there is minimal chance of change and most children become progressively more disabled." Id. Dr. Sherry

recommended seeing a local psychologist for coping and then attending the physical therapy program in Philadelphia. Id.

Mr. Stoev was unable to attend the treatment program in Philadelphia and continued with physical therapy in Florida. Exhibits 5 and 6. Mr. Stoev appeared to be making progress with physical therapy; the records report that his function was improving overall, and he was walking with a straight cane in July 2015. Exhibit 6 at 253. Mr. Stoev visited Dr. Gekht again on August 3, 2015. Exhibit 4 at 33. He reported bilateral leg pain at a moderate level, occurring constantly but improving and relieved by physical therapy and rest. Mr. Stoev reported an overall 60% improvement with physical therapy and no worsening of symptoms. Id. at 35. He discontinued all medication, and Dr. Gekht advised that he continue with physical therapy. Id. On August 14, 2015, Dr. Nickeson also noted that Mr. Stoev was making progress and walking well with a cane. Exhibit 5 at 100.

On December 18, 2015, Mr. Stoev still had allodynia in his legs, as well as vascular changes. Id. at 121. He did not have symptoms in his arms. Id. On December 29, it was reported that he had not used a cane for several days. Exhibit 6 at 419. Mr. Stoev was formally discharged from physical therapy on January 27, 2016. Id. at 442.

On April 22, 2016, Mr. Stoev visited Dr. Nickeson, reporting increased leg pain after his grandmother passed away. Exhibit 5 at 130. The medical records note that there were no color changes in his extremities; his left arm was no longer painful lately; and he was walking well without a cane. They discussed the "unpredictable nature of his condition and the fact that it could completely disappear." Id. at 131.

In June 2016, Mr. Stoev attended a conference in Nashville and was able to walk around with a cane. Exhibit 2 at 3. Then, on August 12, he reported to Dr. Nickeson with increased leg pain after the family dog passed away. Exhibit 5 at 160. He was assessed as having CRPS "with recurrent episodes," and it was noted that "[s]tressful family and environmental situations have been precipitating increases in his symptoms." There was no dramatic allodynia, and he walked fairly well.

Mr. Stoev's mother called Dr. Nickeson on September 15, 2016, requesting additional physical therapy for Mr. Stoev, as she felt he was starting to struggle again. Exhibit 5 at 156. She stated that Mr. Stoev had missed school the other day, and she felt that he would do better if he started physical therapy again. In an affidavit dated September 18, 2019, Dr. Stoev explained the phone call:

> My thinking at that time was based on my observations that [Mr. Stoev] was still living a largely sedentary lifestyle at that point and I hoped that additional physical therapy would help him become more active and healthy.

Exhibit 2 at 4 ¶11.

The doctors retained by the Secretary in this litigation accept that, before vaccination, Mr. Stoev had CRPS. See Exhibit A at 15-16; Exhibit C at 1.

B. Vaccination and Health Afterwards

On September 19, 2016, Mr. Stoev had a routine well-child checkup. Exhibit 9 at 1. He "[had] not had any breakthrough pain at the moment," and was going to school 4 out of 5 days per week. Id. at 2. He was not doing any physical activity, and the doctor recommended at least 5 minutes per day, to be increased as he could tolerate. Id. Mr. Stoev received the Gardasil-9 (HPV-9) vaccine, the Menactra (MCV4) vaccine, and the Hepatitis A vaccine. Id.

Ten days later, Mr. Stoev visited Dr. Daniel Lamar at Coastal Orthopedics for pain in his right ankle following an injury at school. Exhibit 4 at 40. He was put on a short course of oral anti-inflammatories and was to use a brace. Id. at 42.

About three weeks after the vaccination, on October 9, 2016, Mr. Stoev complained of a sudden worsening of pain in his legs. Exhibit 1 at 3; Exhibit 2 at 4. He describes his condition as having "deteriorated dramatically," and he had to go back to using a wheelchair. Id.

After his condition did not improve, Mr. Stoev's mother called Dr. Nickeson's office on October 14 to report that Mr. Stoev was having a flareup. Speaking to Dr. Nickeson's medical assistant, she stated that Mr. Stoev had pain in both legs and was unable to walk. Dr. Stoev also mentioned the recent HPV shot, and asked whether this could be connected. Office staff determined that it would be best for Dr. Nickeson to address the questions upon his return, as he knew Mr. Stoev's case best. Exhibit 5 at 155-56.

Dr. Nickeson spoke with Mr. Stoev's parents on October 25, and learned that Mr. Stoev restarted physical therapy. Exhibit 5 at 153. The parents told Dr. Nickeson their belief that this "current pain episode [was] set off by recent HPV dose 2 weeks before symptoms came on." Id. They stated that they had found a "paper on CRPS induced by HPV in literature." Id.

Mr. Stoev went to Dr. Ashraf Hanna at the Florida Spine Institute on November 10, 2016. Exhibit 11 at 6. He reported pain, hypersensitivity, swelling, and temperature changes in all extremities, and color changes in his lower extremities. Id. As a "Note for New patient," the record from this visit states: "PT RECENTLY HAD THE HPV INJECTION 10/16 THAT CAUSED THE FLARE OF THE CRPS. HAS NOT BEEN CONTROLLED SINCE." Id. (caps in original).

The notes from Mr. Stoev's follow-up appointment with Dr. Nickeson on November 18 state that he had been doing better about 6 months prior, but had "gotten into a serious flare over the past several months." Exhibit 5 at 179-80. Dr. Nickeson noted that Mr. Stoev's symptoms increased with stressful life events, but he had been doing quite well with pain control from December 2015 through March 2016. Id. Mr. Stoev was now unable to bear weight at all, and was having difficulty getting in and out of his wheelchair and typing on a keyboard. The family voiced concerns that physical therapy improvement had stalled, and it was not doing much "in attacking the current pain episode." Id. Dr. Nickeson stated that there was "a plan to do an aggressive approach with ketamine treatments in the next few weeks." Id.

Ketamine treatments were administered in November and December, 2016. Mr. Stoev reported some improvement during the first round of treatment, but his pain worsened again. A second round was administered in February, 2017. There was little improvement during the second round. See Exhibit 11. The family declined additional ketamine treatments. Exhibit 3 at 4.

Between the rounds of ketamine treatments, Mr. Stoev began physical therapy again on January 9, 2017. Exhibit 6 at 486. The record stated that Mr. Stoev had previously returned to normal function, but began having a significant increase in pain and weakness and decreased function and ambulation approximately 2 weeks after receiving the HPV vaccine. Id. The plan was for 4 sessions per week for 12 weeks.

Mr. Stoev saw Dr. Nickeson again on February 24, 2017. Exhibit 5 at 197. Mr. Stoev was described as having "had some good and bad weeks in the past few months." The ketamine treatments were described as "largely unsuccessful" and "did not seem to provide much pain relief." Id. Mr. Stoev was being homeschooled and was still using a wheelchair. He reported increased pain around the right shoulder and upper right leg, and had mild cyanosis of the left foot. Dr. Nickeson recommended continued physical therapy. Id. at 198.

Mr. Stoev had another appointment with Dr. Nickeson on June 2, 2017. Exhibit 5 at 217. He was attending physical therapy four days per week. He still had significant problems with ambulation, significant leg pain with areas of allodynia, and variable erythema on his feet. Dr. Nickeson wrote:

> The parents raised concern today about whether HPV vaccine may have triggered his illness. They found some medical literature on a cluster of cases of complex regional pain syndrome related to HPV vaccination in Japan. Both parents are practicing physicians. I am not familiar with this connection and may have to look up any relevant literature in that area…Regarding relationship of his illness to HPV vaccine, I think without the need for scientific proof of connection to that product, he would likely qualify for consideration through the Federal Vaccine Compensation System. I will help the parents investigate this avenue which could help offset his significant medical care expenses.

Id. at 217-18.

Mr. Stoev's physical therapy records from July 6, 2017 note that he was making some slow progress, especially in his gait and functional abilities. Exhibit 6 at 704. He still had pain in his lower extremities, which limited his functional activities and ambulation. Id. By September, he was going to school in a wheelchair and had poor mobility. He was attending physical therapy for 90 minutes 4 times per week, and could stand for about 40 seconds before his knee would tremble and collapse. Id.

Mr. Stoev visited Dr. Nickeson again on October 6, 2017. Exhibit 5 at 238. He was able to walk with assistance up to 200 feet, but still relied on a wheelchair. His allodynia was in a smaller area, and he continued to have problems in his right thigh, but no particular sensitivity on his trunk, the upper extremities, or the right leg below the knee. Dr. Nickeson wrote:

> I have talked with his parents, who are physicians, before about their concern that his syndrome was induced following a dose of vaccine. I have seen the literature about connection of vaccine products with onset of complex regional pain syndrome and I think that this is something for the scientists to continue working on. However, based on current knowledge, I think that he deserves consideration from the Federal Vaccine Injury Compensation Pool. I will write a letter in support of a request by his parents for his problems to have a hearing in the appropriate forum for the vaccine injury compensation system.

Id. Dr. Nickeson's subsequent letter, dated November 2, 2017, states:

> [Mr. Stoev's] parents called to my attention a series of research studies on low incidence serious adverse events associated with HPV vaccines. This family suspects their son's illness was precipitated by his receiving the HPV vaccine.
>
> Credible researchers in Japan, Sweden, Denmark, and other European centers are actively investigating CRPS in some patients as a vaccine-induced rare disorder. Though the science on this association of [Mr. Stoev's] disabling illness with his preceding use of HPV vaccine is not completely settled, logically he should be a candidate for compensation through the National Vaccine Injury Compensation Program.

Id. at 235; Exhibit 14. Dr. Nickeson provided a list of five articles, which are filed as exhibits in this case.

Mr. Stoev continued with physical therapy, and was attending once per week as of April 25, 2018. Exhibit 6 at 865. He was ambulating with a cane, and reported fatigue at school. His pain was approximately the same with minimal flareups. Id. A note dated June 14, 2018 states that Mr. Stoev appeared to be progressing, with no recent flareups. Id. at 910. He still used a cane to walk, and had an ataxic gait when he walked on a gait belt without an assistive device.

On July 25, 2018, Mr. Stoev was using a wheelchair again and reported a flareup "following an illness," although the nature of this illness was not described. He had not attended physical therapy for two weeks prior to this session. Exhibit 6 at 937. The August 28, 2018 note reports that Mr. Stoev was progressing through the month of August, and was overall doing quite well with his amplified musculoskeletal symptoms. Id. at 962. However, that day he reported increased pain and a flareup that had increased over the last 4-5 days. He could not relate the flareup to any specific activities.

On September 18, 2018, Mr. Stoev again reported increased lower extremity symptoms within the last 4-5 days. Exhibit 6 at 991. He was using a wheelchair and had not been able to walk for the last 1-2 weeks. The physical therapist stated that it "appears that [Mr. Stoev] has suffered a flare up of his discomfort with his amplified musculoskeletal symptoms. Once again, he cannot relate it to any specific mechanism of injury. Our plan is to continue treatment in attempts to increase his functional status to his previous level." Id. Mr. Stoev presented with

aggravated lower extremity pain and weakness a week later, and had "no idea why he [was] getting worse." Id. at 989.

The notes from October 31, 2018 state that Mr. Stoev had continued to report increasing leg pain throughout the month, and that he was still using a wheelchair. Exhibit 6 at 1010. He had been unable to walk for six weeks, and made minimal gains over the last four weeks. Id. Records from November 29, 2018 state that Mr. Stoev was not walking much and became fatigued at school, which he attended 1-2 days per week for a couple of hours at most. Id. at 1042-46.

Mr. Stoev continued physical therapy through summer 2019. Exhibit 31. He was discharged on August 27, 2019 as he was going to college. Id. at 61. His pain levels continued to be high, especially in the lower extremities, but he had improved functionally and was walking with a quad cane up to 400 feet. His rehab prognosis was fair, and he was instructed to schedule physical therapy at college for continued improvement. Id.

Mr. Stoev returned to Lakewood on December 17, 2019. Exhibit 31 at 65. He had not received physical therapy since he left for college in the fall. His main complaints were pain level, decreased gait status, and weakness in all 4 extremities. He was noted to be an excellent candidate for restorative physical therapy, with a good prognosis. He was discharged after seven sessions on December 30, 2019 to return to college. Id. at 72.

Mr. Stoev went again to Lakewood on August 4, 2020 and reported soreness in his back legs. Exhibit 31 at 73. He reported similar levels of pain over the next few weeks. Id. at 74-76. Mr. Stoev continued to report good and bad days with a chief complaint of pain in his lower extremities on September 9, 2020. Id. at 78. He was noted as making progress, but had difficulties scheduling appointments with his class schedule. Id. This was his last formal date of treatment, and no updated records have been filed.

II. Procedural History

Mr. Stoev initiated this case on September 18, 2019, alleging that the HPV vaccine he received on September 19, 2016, caused a significant aggravation of his CRPS. Mr. Stoev filed his petition along with 26 exhibits: affidavits from himself

and each of his parents[2] (Exhibits 1-3); an affidavit and letter from Dr. Nickeson[3] (Exhibits 12 and 14); medical records (Exhibits 4-11); a video from his physical therapy session (Exhibit 13); and medical literature (Exhibits 15-26). Dr. Nickeson opined "that the HPV vaccination was a likely and proximate cause and a substantial factor in the significant aggravation of [Mr. Stoev's] condition and the extension of his symptoms to motor neuron function." Exhibit 12 at 3. Dr. Nickeson cited to studies from "Japan, Sweden, Denmark, and other European countries" but did not put forth a theory of causation. Id.; Exhibit 14.

After reviewing Mr. Stoev's evidence, the Secretary filed his Rule 4(c) Report on March 16, 2020. The Secretary recommended that compensation be denied, arguing that Mr. Stoev had not presented a medical theory causally linking the vaccine to a significant aggravation of his CRPS and had not presented a logical sequence of cause and effect showing that the vaccination was the reason for his injuries. Resp't's Rep. at 8-10. Further, Mr. Stoev had not submitted a report from a qualified medical expert to meet his burden under Loving prongs 4 and 5. Id. at 10. The Secretary requested additional medical and educational records. Mr. Stoev filed a damages affidavit, and the requested records as Exhibits 27-31.

Although the Secretary argued that Dr. Nickeson had not disclosed a theory, leaving a gap in the case, Mr. Stoev rested on Dr. Nickeson's opinion. See Order, issued Nov. 23, 2020; Order, issued Dec. 9, 2020 at 2 n.2. The Secretary declined to respond with an expert, and the parties proceeded to the briefing stage. Id. The parties were advised that, if Mr. Stoev introduced new content, the Secretary could respond. Otherwise, if Mr. Stoev only supplemented his existing theories, the Secretary would be bound by his decision not to retain an expert and could only impeach Dr. Nickeson. Order, issued Dec. 9, 2020 at 2 n.2, 3. The parties discussed the briefing schedule again during a status conference. The undersigned confirmed that Dr. Steven Stoev would be permitted to submit additional articles.

[2] Dr. Steven Stoev and Dr. Muriel Stoev are both licensed to practice in Florida and are both Board Certified in Internal Medicine. Exhibit 2 at 1; Exhibit 3 at 1. They owned a practice in Belgium and worked in an emergency room and intensive care unit. Exhibit 2 at 2; Exhibit 3 at 2. They completed residencies in internal medicine at Louisiana State University, and now have their own internal medicine practice in Florida. Id.

[3] Prior to retirement, Dr. Nickeson worked as a professor, medical director, and practicing clinician for over 40 years. Exhibit 39 at 1. He was licensed to practice in Florida and Board Certified in General Pediatrics and Pediatric Rheumatology. Id.

The Secretary reserved the right to object or respond to any new material. Order, issued Dec. 21, 2020.

On April 28, 2021, Mr. Stoev filed a 44-page brief; a third affidavit from Dr. Nickeson (Exhibit 34); a second affidavit from Dr. Steven Stoev (Exhibit 35); medical articles, and a motion for a ruling on the record. Here, Mr. Stoev advanced the theory that the HPV vaccine aggravated his CRPS through molecular mimicry. Pet'r's Br. at 34; Exhibit 34 at 5; Exhibit 35 at 5.

The Secretary sought leave to file responsive expert reports, arguing that the "updated affidavits substantially and significantly expanded on their prior affidavits, for the first time setting forth a fully articulated theory of causation in their affidavits, discussing medical literature in length, and relying on newly filed medical literature." Resp't's Mot., filed June 18, 2021 at 1.

Mr. Stoev opposed the Secretary's request to file expert reports. Pet'r's Resp., filed June 18, 2021. Mr. Stoev noted that he first filed affidavits from Dr. Stoev and Dr. Nickeson and medical literature with his petition on September 18, 2019, but the Secretary had "consistently and repeatedly declined" to submit expert reports. Id. at 1-2. Mr. Stoev disputed that the recent affidavits presented a new basis for his causation opinion, maintaining that they "merely expound upon what was detailed previously." Id. at 2-4. "Consequently, [the Secretary] already had a fair and full opportunity to address these issues through the submission of expert reports and repeatedly chose not to do so. As such…it is respectfully submitted that 'the Secretary is bound by his previous decision not to retain an expert.'" Id. at 5 (quoting Order, issued Dec. 9, 2020 at 2).

In reply, the Secretary emphasized that his previous decision was based on Dr. Nickeson's "**current**" opinion, but that he had reserved the right to object or respond to new material. Resp't's Reply, filed June 21, 2021 at 2 (quoting Order, issued Dec. 9, 2020 and Order, issued Dec. 21, 2020). The Secretary argued that the most recent affidavits significantly and extensively supplemented the theory of causation by invoking the theory of molecular mimicry for the first time. Id. at 15-21.

Noting that there is "a line between an expert's supplementing a previously disclosed opinion and the expert presenting a new opinion," the undersigned determined that the Secretary had "persuasively explain[ed] why the more recent reports from Dr. Nickeson and Dr. Steve Stoev are new opinions (or at least contain new bases for those opinions)," and, accordingly, the Secretary's retention of experts was justified. Order, issued June 25, 2021.

The Secretary filed a 65-page brief; expert reports from Dr. Carlos Daniel Rose[4] (Exhibit A) and Dr. Stephen J. McGeady[5] (Exhibit C); and medical literature on August 27, 2021. The Secretary and his experts disagreed that molecular mimicry was a viable theory for how the HPV vaccine might aggravate CRPS.

On March 4, 2022, Mr. Stoev filed a 24-page reply brief; another report from Dr. Nickeson (Exhibit 39); a report from Dr. Yehuda Shoenfeld[6] (Exhibit 40); and additional medical literature. Mr. Stoev and his experts maintained that their medical theory was reliable.

Because Mr. Stoev added Dr. Shoenfeld, the Secretary was granted leave to file a sur-reply and supplemental expert reports. See Resp't's Mot., filed May 3, 2022; Order, issued May 17, 2022. The Secretary filed his 19-page sur-reply and supplemental reports (Exhibits H and I) and literature on June 17, 2022. Mr. Stoev filed a 23-page response to the sur-reply, new reports from Dr. Nickeson and Dr. Shoenfeld (Exhibits 42 and 43), and additional medical articles on August 30, 2022. These materials close the record, making the case ready for adjudication.

To adjudicate Mr. Stoev's case, a hearing is not needed. Special masters possess discretion to decide whether an evidentiary hearing will be held. 42 U.S.C.

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[4] Dr. Rose is a board-certified pediatric rheumatologist and Honorary Professor of Pediatrics at Thomas Jefferson University. Exhibit A at 1. Prior to his retirement in 2020, he was a full-time rheumatologist at Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware, and was Chief of the Division of Pediatric Rheumatology between 2004 and 2018. Id. Over his career, he has cared for more than two thousand children with Amplified Pain Syndromes (AMPS), which is a unifying term encompassing CRPS, Reflex Sympathetic Dystrophy, AMPS, and Childhood Fibromyalgia. Id. at 2, 15.

[5] Dr. McGeady is certified by the Board of Pediatrics, the Board of Allergy and Immunology, and the Sub-Board of Clinical Laboratory Immunology. Exhibit D at 1; Exhibit C at 1-2. He was Chief of the Allergy, Asthma & Immunology Division at duPont Hospital for Children in Wilmington, Delaware between 1996 and 2007, and has worked as the Emeritus Chief since 2007. Exhibit D at 1. He is also Professor of Pediatrics at Jefferson Medical College. Id. For ten years, he worked as the medical Director of the Children's Rehabilitation Hospital in Philadelphia, Pennsylvania, and oversaw provision of therapy services to children with multiple types of chronic illnesses. Exhibit C at 2.

[6] Dr. Shoenfeld was the head of the Department of Medicine at the largest hospital in Israel, the Sheba Medical Center, from 1984 to 2011. Exhibit 40 at 1. He founded and headed the Center of Autoimmune Disease there from 1985 to 2018. Id. He was also the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at Tel-Aviv University. Id. Dr. Shoenfeld's clinical and scientific focus is autoimmune/rheumatic diseases, and he has published extensive papers, chapters, and books on the topic. Id. at 1-2.

§ 300aa-12(d)(3)(B)(v) (promulgated as Vaccine Rule 8(c) & (d)), which was cited by the Federal Circuit in Kreizenbeck v. Sec'y of Health & Hum. Servs., 945 F.3d 1362, 1365 (Fed. Cir. 2018). "A special master is not obliged to hold an evidentiary hearing." Oliver v. Sec'y of Health & Hum. Servs., 133 Fed. Cl. 341, 354 (2017), aff'd, 900 F.3d 1357, 1363 (Fed. Cir. 2018).

The parties were informed that the case could be decided without a hearing. Order, issued Dec. 9, 2020. Neither party raised any objections to resolving the case without oral testimony. Mr. Stoev moved for a ruling on the record. Accordingly, adjudication without a hearing is appropriate.

III. Standards for Adjudication

A petitioner is required to establish his case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Hum. Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

As confirmed in W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013), the elements of an off-Table significant aggravation case were stated in Loving. There, the Court blended the test from Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005), which defines off-Table causation cases, with a test from Whitecotton v. Sec'y of Health & Hum. Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resulting test has six components. These are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that

> is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

In resolving claims of significant aggravation, special masters may focus their analysis on the last three prongs of the Loving test, which correspond to the traditional Althen factors. Walker v. Sec'y of Health & Hum. Servs., No. 18-299V, 2022 WL 11141194, at *3 (Fed. Cl. Spec. Mstr. Sep. 27, 2022) (citing Hennessey v. Sec'y of Health & Hum. Servs., No. 01-190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009), mot. for rev. denied, 91 Fed. Cl. 126 (2010)).

IV. Analysis

A. Althen Prong 1 / Loving Prong 4: Medical Theory

The first Althen prong, which corresponds to the fourth Loving prong, requires a petitioner to present a reliable and persuasive medical theory. Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019) (citing Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548 (Fed. Cir. 1994)). To explain how the HPV vaccine can worsen CRPS, Mr. Stoev and his experts have advanced the theory of molecular mimicry. They rely on case series and reports from "Japan, Sweden, Denmark, and other European centers" and submitted case series and reports in support of their theory. Exhibit 14; see also Exhibit 35. These include articles by Blitshteyn, Brinth, Martinez-Levin, Kinoshita, Ozawa, and Hineo/Ikenda on suspected adverse effects to the HPV vaccine. Id. The Secretary and his experts opposed this theory, arguing that an HPV vaccine cannot significantly aggravate CRPS via molecular mimicry. They also called into question the reliability and relevance of the articles submitted by Mr. Stoev. See Resp't's Br. at 21-36.

1. Articles submitted by Mr. Stoev[7]

Many of the case series on which Mr. Stoev and his experts rely have been discussed in the Vaccine Program before, and special masters have repeatedly discredited them. See, e.g., Johnson v. Secretary of Health & Human Services, No. 14-254V, 2018 WL 2051760 at *24 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) (special master reviewing Kinoshita and Ozawa and stating that "many of the items of literature that relied on such case study data were untrustworthy."); Combs v. Sec'y of Health & Human Servs., No. 14-878V, 2018 WL 1581672, at *18 (Fed. Cl. Spec. Mstr. Feb. 15, 2018) (finding the Kinoshita article not persuasive because it involved "a very limited number of case studies"); Balasco v. Secretary of Health & Human Services, No. 17-215V, 2020 WL 1240917, at *32 (Fed. Cl. Spec. Mstr. Feb. 14, 2020) (after reviewing the Kinoshita, Brinth, Martinez-Levin, Ozawa, and Blitshteyn articles, as well as additional evidence, the special master did not find "preponderant evidence . . . that the above-discussed literature, considered individually or as a whole, provides a basis for [Ms. Balasco] to assert a claim for an adverse reaction to her HPV vaccine."); Cottingham v. Sec'y of Health & Hum. Servs., No. 15-1291V, 2021 WL 6881248, at *39-43 (Fed. Cl. Sept. 27, 2021) (recognizing that special masters have found Ozawa and Kinoshita "not sufficiently persuasive to assist any petitioners in meeting their burden to show, by a preponderance of the evidence, the HPV vaccine can cause different injuries."), mot. for rev. denied, 159 Fed. Cl. 328 (2022), appeal docketed No. 2022-1737 (Fed. Cir. Apr. 28, 2022); E.S. v. Sec'y of Health & Hum. Servs., No. 17-480V, 2020 WL 9076620, at *44 (Fed. Cl. Nov. 13, 2020) (describing Ozawa and Kinoshita as "wanting" with regards to showing an HPV relationship to POTS and autonomic dysfunction generally, and noting that Ikeda did not demonstrate that the autonomic system-impacting autoantibodies were caused by vaccination, or even likely pathogenic), mot. for rev. denied, 154 Fed. Cl. 149 (2021); America v. Sec'y of Health & Hum. Services, No. 17-542V, 2022 WL 278151 at *9 (Fed. Cl. Jan. 4, 2022) (Martinez-Levin and Kinoshita "do not stand as robust proof in support of causation"); see also id. at *33 (noting that these articles have repeatedly "been deemed unreliable or unpersuasive"); Brunker v. Sec'y of Health & Hum. Servs., No. 18-683V, 2023 WL 21255, at *9 (Fed. Cl. Jan. 3, 2023) (stating that the Blitshteyn and Ozawa articles "would not meet petitioner's preponderant burden of proof" that the HPV vaccine caused the reported symptoms).

[7] Bibliographic information for the articles cited in this decision is found in the appendix.

This set of literature does not stand as persuasive evidence for Mr. Stoev's theory that the HPV vaccine can aggravate CRPS.

2. Epidemiology

Epidemiology is a method by which medical researchers determine whether an exposure to a substance changes the incidence of a condition. Mr. Stoev filed a report by Chandler and colleagues critiquing epidemiological studies. The Secretary filed several epidemiological studies to rebut Mr. Stoev's case series.

a) Mr. Stoev's Exhibit

Chandler. The Chandler authors reviewed global reporting patterns for HPV vaccine for subgroups of reports with similar adverse event profiles. Chandler (Exhibit 17) at 81. The researchers hypothesized that different reporters may use different terms to describe different conditions (e.g., CRPS, POTS and chronic fatigue syndrome), but that there might be enough overlap to identify subgroups of HPV vaccine reports with similar adverse event profiles. Id. at 82. Using VigiBase (the WHO international database of suspected adverse drug reactions), the authors identified 39,993 individual reports for HPV vaccines to January 1, 2015 and sorted them into 4116 clusters via an algorithm. Id. at 83. Fifty-four of the clusters had 5 or more reports. Id. The analysis revealed "a large number" of reports with a pattern of adverse events including headache, dizziness, fatigue, and syncope. Id. at 85. The majority of reports lacked explicit diagnoses. Id. at 86. The authors stated: "our analyses suggest that the combination of headache and dizziness with either fatigue or syncope is reported significantly more often in HPV vaccine reports compared with non-HPV vaccine reports for females aged 9-25; this disproportionality remains when results are stratified by age and when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) are excluded." Id.

Dr. Rose critiqued Chandler in his first report. Exhibit A at 25-26. As he stated, the "vague" symptoms studied (fatigue, dizziness, headache, and syncope) were found more frequently even when the conditions of interest (CRPS, CFS, and POTS) were not reported. Id. at 25. "In summary, the fact that these extremely unspecific symptoms listed in the criteria for CFS, CRPs, and POTS appear more frequently does not mean that the conditions are more frequently reported after HPV." Id. at 26. The Chandler researchers themselves recognized that their study did not establish a causal relationship. Chandler at 9. Dr. Rose also noted that Chandler excluded case series from Japan and Denmark (Kinoshita and Brinth) because of the "high proportion of reports." Exhibit A at 24 (citing Chandler at 5).

In support of Chandler, Mr. Stoev summarized its findings and stated only that "This finding was also reinforced by Martinez-Levin, et al." Pet'r's Br. 39-40. Dr. Nickeson did not defend the article beyond questioning Dr. Rose's credibility for criticizing Mr. Stoev's submissions. Exhibit 39 at 7.

b) The Secretary's Exhibits

Huygen. Via Dr. Rose, the Secretary presented this article to "illustrate the significant limitations with the Kinoshita, et al. article." Resp't's Br. 58. Huygen and colleagues conducted a "Rigorous review of all potential CRPS cases reported to GSK (a vaccine manufacturing company) since launch of HPV-16/18-adjuvanated vaccine [and] identified five cases considered by independent experts to be confirmed CRPS." Huygen (Exhibit A-8) at 1118. Quantitative analyses did not suggest a higher rate of CRPS reporting after the HPV vaccine than other vaccines. Id. The researchers specifically discussed their review of the Kinoshita case series, that none of the cases fulfill the CRPs diagnostic criteria (Japanese or Budapest), "which raises the question of how the diagnostic criteria were applied." Id. They further note that the Kinoshita researchers describe POTS, OH, and low plasma levels of noradrenaline in some patients. Id. While low levels of noradrenaline are found in CRPS, most CRPS patients do not have POTS and OH. Id. "Moreover, the sympathetic dysfunction is typically local and distal in one of the extremities and in no way general (Wasner, 2010), as seems to be the case with the girls described in the article." Id. The Huygen authors conclude their paper by stating: "based on the outcomes of this valuation, there is not sufficient evidence to suggest an increased risk of developing CRPS following vaccination with HPV-16/18-adjuvanated vaccine." Id. at 1119. Neither Mr. Stoev nor his experts addressed this study.

EMA. The European Medicines Agency reviewed reports of CRPS and POTS in young women aged 10-19 who received the HPV vaccine. EMA Report (Exhibit A-10) at 1. The EMA confirmed "that the evidence does not support a causal link between the vaccines (Ceravix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS." Id. The "review included published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States." Id. The Agency summarized:

> A careful review looking at all the available evidence has concluded that the occurrence of CRPS and POTS in vaccinated girls is no higher than would be expected in girls in the general population . . . and that there is no evidence that the vaccine can trigger these syndromes. The

> review took into account . . . a variety of possible scenarios for underreporting and reports that did not fully meet diagnostic criteria for these syndromes.

Id. at 2, 3. These findings were passed to the Agency's Committee for Medical Products for Human Use, which concurred that the available evidence does not support that HPV vaccination caused CRPS and POTS. Id. at 2. The Committee did not recommend any changes to the terms of licensing or product information and passed its position to the European Commission for a legally binding decision.

WHO. The World Health Organization Global Advisory Committee on Vaccine Safety expressed concerns about the Japanese case series discussing CRPS and POTS following HPV vaccination. WHO Report (Exhibit A-9) at 6. The Committee stated that these "are both disorders of unclear and possibly heterogeneous etiology and the epidemiology is not well characterized." Id. Further, "Despite the difficulties in diagnosing or fully characterizing CRPS and POTS, reviews of pre- and post-licensure data provide no evidence that these syndromes are associated with HPV vaccination." Id. The Committee also noted that "Review of clinical data by the national expert committee led to a conclusion that [chronic pain and other symptoms] were not related to the vaccine." Id. In an extract from a later meeting, the Committee reported that it had reviewed case reports of CRPS and POTS associated with HPV vaccination from Denmark and Japan. Id. at 1-2. "The Committee concluded that since their last review, there is still no evidence to suggest a causal association between HPV vaccine and CRPS, POTS, or the diverse symptoms that include pain and motor dysfunction." Id. at 2.

Dr. Rose characterized the World Health Organization and the European Medicines Agency as "two of the most reputable governmental organizations in health care." Exhibit A at 31. As he notes, both reports "deny any credibility" to the claims from the case series from Japan and Denmark (Brinth, Kinoshita, Ozawa, Ikeda/Hineo) "in unequivocal terms." Id. at 32. Neither Mr. Stoev nor his experts address these governmental reports.

Vielot. The Vielot researchers studied the potential association between the HPV vaccine and CRPS in adolescent girls in the United States. Vielot (Exhibit C-7) at 108. Using medical claims from the IBM MarketScan Commercial Database between June 29, 2006 and December 31, 2014, the researchers analyzed a cohort of 1,232,572 girls who turned 11 years old during the study period; had no prior claims for HPV vaccination or CRPS; and had at least one year of continuous insurance plan enrollment prior to their 11th birthday. Id. at 109. Of this cohort, they identified 563 CRPS cases. Id. at 110. The researchers estimated the relative

30, 90, and 180-day hazards of CRPS following HPV vaccination. They also factored in the pre-existing comorbidities. Id. at 108, 112. To improve the efficiency of the models for estimating the relative hazard of CRPS, the researchers created a sub-cohort, which included all CRPS cases and a random 10% sample of the full cohort. Id. at 109. The case-cohort sample size was 123,981. The authors found that "The hazard of CRPS was not significantly elevated in the days following HPV vaccination, irrespective of the number of doses received and the length of time elapsed since vaccination, and [they] identified a large number of health-related predictors of CRPS among adolescent girls." Id. at 111. The authors further note that their results were consistent with the EMA and WHO results. Id.

Hviid. The researchers in Hviid evaluated 869 patients with autonomic dysfunction syndromes from a cohort of 1,375,737 Danish females between the ages of 10-44. Hviid (Exhibit C-6) at 1. Of these patients, 535 were identified as having CRPS. The researchers concluded that HPV vaccination "did not statistically significantly increase the rate of a composite outcome of all syndromes with autonomic dysfunction in a 365 day risk period following vaccination," or the rate of chronic fatigue syndrome, CRPS, or POTS individually. The researchers state: "Although we cannot formally exclude the possibility of an increased risk of up to 32%, a larger increase in the rate of any syndrome associated with vaccination is unlikely given the statistical power of our study." Id. at 7.

Dr. McGeady submitted the Hviid and Vielot papers, describing them as "well designed epidemiological studies comparing large groups of Gardasil recipients and control subjects [which] have not found an increase in CRPS in recipients of [the] HPV vaccine." Exhibit C at 5.

Dr. Nickeson argued that such large-scale studies look for mean values and frequent events, and can therefore easily miss extremely rare events such as Mr. Stoev's. Exhibit 39 at 12. Because of its built-in error factor, Dr. Nickeson contended that the Hviid study "cannot provide any conclusive weight against supposing [Mr. Stoev] had an [adverse event] which they did not recognize in their cohort." Id. He further noted the authors' acknowledgement that "increased risk of up to 32% cannot be excluded by this study." Id. at 13. Dr. Nickeson also stated that "there is a similar statistic argument to be made" about the Vielot paper, noting its 95% confidence interval: "by definition there is a 5% chance your analysis is wrong (ie: 1 chance out of 20)." Id.

In response, Dr. McGeady maintained that these studies are relevant, as they found no epidemiological association between the HPV vaccination and CRPS. Exhibit I at 3. While the studies "do not completely rule out a rare adverse event . .

. they do not support [the] proposed immunopathologic mechanism of molecular mimicry," which requires evidence of an epidemiological association. Id. In his responsive report, Dr. Nickeson pointed out that neither study used Gardasil 9 and that both studies used only female subjects. Exhibit 42 at 7. "In a great number of medical disorders, gender differences are recognized. As such, these studies seem tangential to the present circumstances." Id.

c) Assessment

As discussed above, the cases series filed by Mr. Stoev lack persuasive value on their own. They are further undermined by the studies submitted by the Secretary. Huygen critiques the Kinoshita article (which is cited by Martinez-Levin and Blitshteyn)[8], and found no elevated risk of CRPS following HPV vaccination. Huygen has been discussed in the Vaccine Program before, and was found to "directly undercut" a petitioner's arguments about CRPS and its association with the HPV vaccine. Hughes v. Sec'y of Health & Hum. Servs., No. 16-930V, 2021 WL 839092, at *33 (Fed. Cl. Jan. 4, 2021), mot. for rev. denied, 154 Fed. Cl. 640 (2021). The WHO and EMA were also conducted in response to case series from Japan and Denmark, and refute the results reported in the literature filed by Mr. Stoev. Neither Mr. Stoev nor his experts addressed Huygen, the EMA report, or the WHO report.

Dr. Nickeson questioned the relevance and reliability of Hviid and Vielot for their use of only female patients; for not covering the Gardasil 9 vaccine (which Mr. Stoev received); and for their margins of error. Notably, several of the case series submitted by Mr. Stoev (Kinoshita, Ozawa, Hineo/Ikeda, Brinth) also only report on female subjects, and 98% of the Martinez-Levin participants were female. Martinez-Levin at 1982. Chandler also only analyzed reports from females. Chandler at 83, 85. Dr. Nickeson might have enhanced any point regarding the commonness of females in studies about the safety of the HPV vaccine if he connected a difference in gender to CRPS, the condition afflicting Mr. Stoev.

Likewise, while Hviid and Vielot did not study the Gardasil 9 vaccine, many of Mr. Stoev's case series do not discuss it either. See Hviid at 3 (quadrivalent

[8] Additionally, the patients in Kinoshita, Ozawa, and Hineo/Ikeda overlap. Kinoshita participants were hospitalized at the Shinshu University School of Medicine between June 2013 and 2014. Kinoshita at 2186. Hineo participants were hospitalized at this same institution between June 2013 and September 2016, and Ozawa patients between June 2013 and December 2016. Hineo at 2; Ozawa at 1221. The Hineo researchers note this overlap. Hineo at 1.

vaccine); Vielot at 109 (bivalent and quadrivalent vaccines); see also Brinth at 1 (quadrivalent vaccine); Martinez-Levin at 1982 (quadrivalent and bivalent vaccines); Kinoshita at 2185 (quadrivalent Gardasil and Ceravix); Ozawa at 1219 (quadrivalent Gardasil and Ceravix); Hineo/Ikeda at 2 (quadrivalent Gardasil, Ceravix, and one unknown). Chandler did not specify which vaccines were included in the analysis but mentioned the European approval of the quadrivalent Gardasil and bivalent Ceravix. Chandler at 82.

The EMA and WHO reports, on the other hand, did include Gardasil 9. See WHO Report at 3 n.25 (citing study of nine-valent vaccine); EMA Report at 3 (Gardasil/Silgard, Gardasil 9, and Ceravix). Although the EMA report appears to focus primarily on female patients, the WHO report discusses reports of symptoms "in both sexes" and refers to studies involving "individuals" and "persons" rather than exclusively women or girls. WHO Report at 2-3. These large-scale epidemiological studies, which carry more weight than case series, found no association between the HPV vaccines and CRPS. Mr. Stoev and his experts did not dispute the reliability or relevance of these reports.

"While it is true that petitioners are not obligated to offer epidemiologic evidence to support their claim, it can be considered (especially when it exists and is especially relevant to the causal theory at issue) in evaluating the success of a Vaccine Act petitioner in meeting her evidentiary burden." Johnson, 2018 WL 2051760, at *25. The case series and reports submitted by Mr. Stoev – some of which were alluded to and criticized in the WHO and EMA reports – do not effectively rebut the Secretary's epidemiologic evidence. Taken together, the epidemiologic evidence weighs against finding that the HPV vaccination either causes or aggravates CRPS. Some of the epidemiologic studies involved more than one million participants, a number than enhances the likelihood that an adverse reaction would have been detected. Moreover, some of the epidemiologic studies were directed to the disease at issue in Mr. Stoev's claim, CRPS. This specificity also increases the value of the epidemiologic evidence.

However, a petitioner can receive compensation even in the absence of epidemiologic studies. Thus, the theory of molecular mimicry is addressed next.

3. Molecular Mimicry

a) Appellate Precedents regarding Molecular Mimicry

Because special masters are often called upon to evaluate the persuasiveness of the theory of molecular mimicry, the Court of Federal Claims and the Court of

Appeals for the Federal Circuit have considered molecular mimicry in their appellate role. In December 2019, the undersigned identified the leading precedents as W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352 (Fed. Cir. 2013), and Caves v. Sec'y of Dep't. of Health & Hum. Servs., 100 Fed. Cl. 119 (2011), aff'd sub nom., 463 F. App'x 932 (Fed. Cir. 2012). Tullio v. Sec'y of Health & Hum. Servs., No. 15-51V, 2019 WL 7580149, at *12-14 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448 (2020). While Tullio describes those cases in more detail, their essence appears to be that although molecular mimicry is accepted in some contexts, special masters may properly require some empirical evidence to show that a particular vaccine can cause a particular disease.

In the next approximately three years, appellate authorities reviewing decisions involving molecular mimicry have generally endorsed the approach of looking for some evidence that persuasively shows that a portion of a vaccine resembles a portion of human tissue, which contributes to causing the disease, and that the immune system will respond to the relevant amino acid sequence.[9] Chronologically, the list of more recent appellate cases begins with the opinion in Tullio, which denied the motion for review. 149 Fed. Cl. 448, 467-68 (2020).

Another example in which the Court of Federal Claims held that the special master did not elevate the petitioner's burden of proof in the context of evaluating the theory of molecular mimicry is Morgan v. Sec'y of Health & Hum. Servs., 148 Fed. Cl. 454, 476-77 (2020), aff'd in non-precedential opinion, 850 F. App'x 775 (Fed. Cir. 2021). In Morgan, the Chief Special Master found that petitioner had not presented persuasive evidence about a relevant antibody. Id. at 477. The Chief Special Master also noted that the articles about the relevant disease do not list the wild flu virus as potentially causing the disease. Id. When examining this analysis, the Court of Federal Claims concluded: "the Chief Special Master did not raise the burden of causation in this case; petitioner simply failed to meet it." Id.

The Federal Circuit also evaluated the Chief Special Master's approach in Morgan. The Federal Circuit concluded: "We discern no error in the special master's causation analysis." 850 F. App'x 775, 784 (Fed. Cir. 2021).

Most other recent appellate cases follow this path. See, e.g., Duncan v. Sec'y of Health & Hum. Servs., 153 Fed. Cl. 642, 661 (2021) (finding the special

[9] The term "homology" is used when discussing molecular mimicry. "Homology" is defined as "the quality of being homologous; the morphological identity of corresponding parts; structural similarity due to descent from a common form." *Dorland's* at 868.

master did not err in rejecting a bare assertion of molecular mimicry); Caredio v. Sec'y of Health & Hum. Servs., No. 17-79V, 2021 WL 6058835, at *11 (Fed. Cl. Dec. 3, 2021) (indicating that a special master did not err in requiring more than homology and citing Tullio); Yalacki v. Sec'y of Health & Hum. Servs., 146 Fed. Cl. 80, 91-92 (2019) (ruling that special master did not err in looking for reliable evidence to support molecular mimicry as a theory); but see Patton v. Sec'y of Health & Hum. Servs., 157 Fed. Cl. 159, 169 (2021) (finding that a special master erred in requiring petitioner submit a study to establish medical theory causally connecting flu vaccine to brachial neuritis).

The parties' arguments on molecular mimicry are summarized.

b) Expert Reports

Mr. Stoev's initial set of expert materials regarding molecular mimicry came from Dr. Nickeson and Mr. Stoev's father, Dr. S. Stoev.

Dr. Nickeson stated "that molecular mimicry is a viable medical theory causally connecting [Mr. Stoev's] worsened condition to the subject vaccination." Exhibit 34 at 5. He explained that "since the nature of all vaccines is to induce antibody production, the theory of molecular mimicry is applicable to HPV and CRPS patients such as [Mr. Stoev]." Id. at 6. He cited various articles, including a 2018 article by Dr. Yahel Segal and Dr. Shoenfeld, explaining the relevance of shared peptides. Segal & Shoenfeld (Exhibit 34-1). The article discusses autoimmunity suspected to be induced by the flu, hepatitis B, and HPV vaccines. Id. at 1. The authors state that the vast homology between viral and bacterial elements and the human proteome may at times promote immune tolerance, but may also facilitate pathologic autoimmune processes such as molecular mimicry, "wherein an immune reaction directed against foreign pathogenic elements, bearing similarity to human proteins, may evolve into an autoimmune process targeting the homologous self-proteins." Id. at 6.

Dr. S. Stoev also advanced the theory of molecular mimicry, summarizing that autoantibodies with agonistic effects on receptors in the autonomic nervous system "could help explain the development or exacerbation of autonomic dysfunction described in many patients with suspected side effects to the HPV vaccine through the process of molecular mimicry." Exhibit 35 at 5. Dr. Stoev submitted various articles (Blaes, Kohr, Knudsen) in support of the contention that CRPS may be autoimmune.

The Secretary's experts disagreed that the HPV vaccine could aggravate CRPS via molecular mimicry. Dr. Rose primarily discussed why this theory was not persuasive for Mr. Stoev's CRPS, concluding: "That is a non-autonomic clinical stage ostensibly resulting from an autonomic pathogenesis. I am afraid this argument lacks biological plausibility in its essence." Exhibit A at 22.

Dr. McGeady acknowledged that molecular mimicry is a proposed basis for many diseases but cautioned against using data from experiments on animals uncritically to human disease. Exhibit C at 2. He quoted a paper by Albert & Inman concluding: "No data convincingly demonstrate that molecular mimicry is an important mechanism in the development of autoimmune disease in humans." Id. Dr. McGeady also criticized Segal & Shoenfeld and their theory that similarity between shared peptides forms the basis for mimicry. Citing Kanduc, Dr. McGeady explained:

> [The Kanduc investigators] noted that after studying a number of common viruses the sharing of pentapeptides between viral and human proteomes is so common that the prevalence of autoimmune disease would approach 100% if molecular similarity led to autoimmunity. The explanation of why these shared pentapeptides do not elicit autoimmunity may lie in the fact that the three dimensional structure of the shared sequences is different. Since the immune system recognizes antigens partly by their spatial configuration, identical peptide sequences inserted in different proteins may be folded into very divergent shapes, thus appearing dissimilar to immune cell receptors.

Exhibit C at 3 (internal citations omitted). Dr. McGeady concluded that molecular mimicry between vaccine antigens and host epitopes was not a plausible explanation for the injury, and that the theory "fail[ed] to causally connect the vaccination to the injury." Id.

In response, Mr. Stoev submitted a report from Dr. Shoenfeld. Dr. Shoenfeld argued for an autoimmune etiology of CRPS, stating that "the role of the autonomic nervous system in the manifestation of CRPS has been widely documented yet not fully established," and cited to studies "suggesting an autoimmune nature" of CRPS. Exhibit 40 at 4-5. He highlighted a study by Goebel et al. which coined the term "IRAM" to denote "injury-triggered, regionally restricted, autoantibody-mediated autoimmune disorder with minimally destructive course." Id. at 5.

Noting that CRPS is characterized by pain as a dominant symptom, Dr. Shoenfeld used the Immune Epitope Database (IEDB) to identify 32 pentapeptides shared between the HPV vaccine and human proteins throughout 18 pain-related proteins. He pointed out that many of the pentapeptides listed have immunogenic potential. Exhibit 40 at 7-10.

In response to Dr. McGeady's argument that the prevalence of autoimmune disease would approach 100% if molecular similarity led to autoimmunity, Dr. Shoenfeld cited a different paper by Kanduc, stating: "molecular mimicry by itself cannot be the cause of autoimmunity under normal physiological conditions since the immune system is under the protection of immune tolerance mechanisms." Exhibit 40 at 12. Rather, vaccine adjuvants hyperactivate the immune system. "Molecular mimicry unavoidably triggers cross-reactivity and harmful autoimmunity under particular conditions (i.e., vaccine adjuvanation or in certain individuals like [Mr. Stoev] who were already within a susceptible population at the time of administration) that disrupt the host's immune tolerance and evoke cross-reactive attacks against self proteins and self tissues." Id. at 13.

Addressing Dr. McGeady's contention that shared pentapeptides do not elicit autoimmunity because the three-dimensional structure of the shared sequences is different, Dr. Shoenfeld referenced another paper by Kanduc. The paper documents that the immunogenic/antigenic potential of pentapeptides varies as a function of their hydrophobicity – a main property required for a pentapeptide to be an epitope. Exhibit 40 at 13-14. Hydrophobicity, argued Dr. Shoenfeld, is a filter that determines whether a peptide will be bound by the B cell receptor. Id.

The Secretary's experts challenged Dr. Shoenfeld's opinions. Dr. Rose argued that, even assuming the biological plausibility of the theory that agonist antibodies may generate in response to injuries in some percentage of CRPS patients, the HPV vaccine would play no role in autoimmune CRPS. Exhibit H at 12-13. Dr. Rose reviewed Dr. Shoenfeld's table of shared pentapeptides and found that "the alleged 'pain related proteins' have no direct connection with the regional pain mechanism proposed by the autoimmune theory (IRAM) of CRPS." Id. at 13-14. Some of the proteins are "intracellular and could not be bound (in general) by autoantibodies." Id. at 14. Additionally, Dr. Rose stated that Dr. Shoenfeld provided no evidence that the identified peptides can bind relevant MHC (hla-II) alleles. "[T]he simple listing of homology and putative human targets after a database search falls extremely short of a true theory of mimicry." Id. at 15. Dr. Rose noted that later work from Kanduc found that "peptide homology is not only not sufficient to explain mimicry, but in fact could induce the opposite effect (tolerance)." Id., citing Kanduc (Exhibit H-5).

Dr. McGeady stated that the cause of CRPS is idiopathic and not known to be autoimmune; but, even supposing that autoimmunity is the cause of CRPS, he did not agree with Dr. Shoenfeld's hypothesis. Exhibit I at 4. Given that "there is extensive sharing of peptides between viruses and human proteins," the "[i]dentification of concordance between a peptide and a viral vaccine and in human proteins is not unexpected, and despite the epitope being represented in the IEDB does not provide evidence that it is likely to produce and autoimmune disease." Id. He again highlighted "the frequency of mimics between viral and human proteins, and by inference the relative infrequency of autoimmune disease associated with viral infections." Id. Dr. McGeady characterized the idea that adjuvants may incite autoimmunity as "unproven and conjectural," and noted that "[a]ll vaccines currently in use contain adjuvants." Id. at 5.

Dr. McGeady questioned the relevance of Dr. Shoenfeld's point about the hydrophobic vs. hydrophilic properties of pentapeptides being determinant of whether they will be bound by B cell receptors and processed for presentation to T cells. He explained:

> Unlike the T cell, the B cell receptor binds cognate antigens without their having to be processed by being internalized into other [antigen presenting cells]…therefore the epitopes may be displayed on macromolecules as they are ligated, and it is unlikely that their hydrophobic properties are independent of those macromolecular structures.
>
> While it is known that B cells can function as antigen presenting cells (APC) they are not the sole or even the principal APCs…[and we] do not know whether the immune receptors of those non B cell APCs possess the same properties of favoring hydrophobic epitopes for presentation to T cells, nor do we know whether the T cell receptor has such properties…
>
> There is evidence that T cell receptor binding is dependent on configuration of the epitope and that the sequence of the amino acids matters less than the structural similarity of the epitope.

Exhibit I at 5.

In response, Dr. Shoenfeld took issue with Dr. McGeady's use of the word "idiopathic," stating that it "appears condescending to suggest that we do not know the pathology." Exhibit 43 at 2. He maintained that viruses could cause CRPS and

stated that he found 57 papers on Pub-Med "alluding to viruses as a cause of CRPS," and many "also refer to the recent COVID-19." Exhibit 43 at 3. He listed a sample of his search results. Id. at 3-4.

Dr. Shoenfeld again contended that autoantibodies can induce pain. He referenced a paper by Goebel et al. in which mice were treated with immunoglobulin (IgG) from patients with fibromyalgia syndrome. The researchers concluded that the IgG produces painful sensory hypersensitivities by sensitizing nociceptive afferents. Exhibit 43 at 4-5. According to Dr. Shoenfeld, this shows "that the autoantibodies bind to the dorsal synapse and can induce high sensitivity to external stimuli etc." Id. at 4. Dr. Shoenfeld stated that Goebel and his team extended this study in a paper entitled "Clinical trial: A CRPS-IgG-transfer-trauma model reproducing inflammatory and positive sensory signs associated with [CRPS]." Id. at 5. Another study by Guo et al. involved "a very similar passive transfer" and concluded that "Autoimmunity plays a key role in the progression of nociceptive and vascular changes in the mouse fracture model and potentially contributes to the CRPS disease process." Id. Dr. Shoenfeld argued that these studies demonstrate that the "autoantibodies directed against the autonomic nervous constituents are PATHOGENIC. Their passive transfer to naïve mice can induce the clinical picture of CRPS and similar conditions." Id.

Dr. Shoenfeld concluded that the "conceivable theory of molecular mimicry" supported by a time relationship, contrasted with "the absence of plausible theories for pathogenesis" from the Secretary, indicated that it was "more probable than not" that the HPV vaccine caused Mr. Stoev's CRPS aggravation. Exhibit 43 at 6.

c) Assessment

The record, when considered as a whole, does not support a finding that Mr. Stoev has met his burden of establishing with preponderant evidence that molecular mimicry is a persuasive theory to explain how an HPV vaccination can worsen CRPS. Specific problems include: (1) the problems with epidemiology; (2) the commonness of homology between viruses and human proteins; (3) the failure of Mr. Stoev and Dr. Shoenfeld to establish with preponderant evidence that the homology is relevant to CRPS; and (4) the failure of Mr. Stoev and Dr. Shoenfeld to link the HPV vaccine to agonist antibodies.

First, under the preponderance of evidence standard, a theory must be "sound and reliable." Boatmon, 941 F.3d at 1359 (quoting Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)). As discussed

above, large epidemiologic studies conducted by the EMA and WHO did not detect an increased incidence of CRPS among people who received the HPV vaccine. The Chandler article found a higher rate of symptoms related to POTS, CRPS, and CFS following HPV vaccination, but acknowledged that a causal association "remains uncertain" and called for "a more definitive study of the findings." Chandler at 9. On balance, these epidemiologic studies undermine the reliability of the theory of molecular mimicry between the HPV vaccine and human proteins as a cause of CRPS.

The second problem relates to homology. Dr. Shoenfeld summarized: "We claim that the vaccine of HPV caused the aggravation of the CRPS of [Mr. Stoev]. The mechanism is molecular mimicry, as shown by many peptides (see Tables in my last reports) and inductions of autoantibodies to the autonomic nervous system which led to the 'autoimmune pain.'" Exhibit 43 at 2. However, "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." Tullio, 2019 WL 7580149, at *15. As the Secretary's experts explained, there is extensive commonality between viruses and human proteins. To prevail on a theory of molecular mimicry, a petitioner must "offer reliable and persuasive medical or scientific evidence of some kind (whether expert testimony or literature) that suggests the vaccine components could interact with the self structures as maintained." Johnson, 2018 WL 2051760, at *26.

Dr. Shoenfeld makes the conclusory statement, "We have summarized extensively the molecular mimicry existing between the HPV virus and many molecules existing on the nerves and nerve endings leading to the generation of 'autoimmune pain.'" Exhibit 43 at 2. In support of this statement, Dr. Shoenfeld cited to two articles by Goebel (Exhibits 43-1 and 43-2) on autoimmune pain. However, neither article discusses molecular mimicry or the HPV virus or vaccine. Dr. Shoenfeld has not substantiated his assertion that molecular mimicry between the HPV vaccine and human proteins is "shown by many peptides." As stated, the sharing of peptides is not uncommon, and therefore does not establish the occurrence of molecular mimicry.

Third, although Dr. Shoenfeld stated that the peptides shared between the HPV vaccine and human proteins are related to pain, he did not refute Dr. Rose's argument that they have no direct connection to the regional pain mechanism proposed by the IRAM theory of CRPS, and are not necessarily accessible to antibodies. Exhibit 40 at 8-10; Exhibit H at 13-14. Dr. Shoenfeld later cited mouse studies suggesting that antibodies may play a role in the pathogenesis of CRPS, but these studies did not link those agonist antibodies to the shared pain-related proteins Dr. Shoenfeld previously identified. See Exhibits 43-12, 43-13,

and 43-14. With this, there remains a disconnect between the shared peptides and the pain mechanism relevant to an autoimmune theory of CRPS.

Fourth, and relatedly, Mr. Stoev and Dr. Shoenfeld did not offer evidence that the HPV vaccine has been established to cause the agonist antibodies to generate. The mouse studies cited by Dr. Shoenfeld associate the agonist antibodies with CRPS, but they do not mention the HPV virus or vaccine, or molecular mimicry. This is another vital gap in the theory.

Overall, the gaps and unexplored assumptions in Dr. Shoenfeld's theory that molecular mimicry can worsen CRPS are too much for Mr. Stoev to overcome, and he has not presented sufficient evidence to make this theory persuasive. Thus, he has not presented preponderant evidence, and has not met his burden under Althen prong 1/ Loving Prong 4.

A finding that a petitioner has not met one element of the Althen prongs justifies a denial of compensation. However, assuming that Mr. Stoev had proposed a reliable theory of what can happen – a vaccine-induced, autoimmune trigger for aggravated CRPS symptoms – he has not presented preponderant evidence that this happened to him. As described below, the evidence supports a finding that Mr. Stoev's CRPS was non-autoimmune in nature, and the record indicates that the onset of the aggravation at issue predated his vaccination. These topics are explored in sections B and C below.

B. Loving Prong 5 / Althen Prong 2

1. Law / Elements

Pursuant to Althen, a petitioner must establish "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. A petitioner does not need to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" to satisfy this prong, but may rely on circumstantial evidence and reliable medical opinions. Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325-26 (Fed. Cir. 2006).

2. Opinions Generated in the Course of Medical Treatment

a) Overview of Treating Doctors' Statements

The Federal Circuit has instructed special masters to carefully consider the views of treating doctors. Capizzano, 440 F.3d at 1326. Dr. Nickeson has treated Mr. Stoev for his CRPS since his onset in 2015. Prior to retirement, Dr. Nickeson was a board-certified pediatric rheumatologist. Exhibit 34 at 1. Mr. Stoev's parents, who are physicians, were his primary care providers. Pet. at 3. Mr. Stoev's parents run their own practice and are board-certified in internal medicine. Exhibit 2 at 1-2; Exhibit 3 at 2-3.

Dr. Muriel Stoev averred:

> By October 14, 2016, when [Mr. Stoev's] condition had not improved, we called Dr. Nickeson to report his situation. At that time, since the change in his condition was so dramatic and since from a clinical standpoint the vaccination he received was the only thing that happened to [him] during that time period, we had already started suspecting that the vaccination he received was the impetus for the significant aggravation of his condition.

Exhibit 2 at 4. Likewise, Dr. Steven Stoev stated:

> Clinically, we became suspicious that he was having an adverse reaction to the vaccination fairly early on. There was simply no other inciting event or circumstance during that time period which would cause or provoke such a dramatic and deleterious response in his condition.

Exhibit 3 at 4. The Stoevs then began to review medical literature, and "[a]fter reading some of the articles and case studies reported on the HPV vaccine, [they] became even more convinced that the administration of the HPV vaccine that day was the inciting event that caused a significant aggravation in [Mr. Stoev's] condition." Exhibit 2 at 4-5; see also Exhibit 3 at 4-5.

Notes from Mr. Stoev's October 25, 2016 appointment with Dr. Nickeson indicate that the Stoevs raised these concerns to him, and mentioned that they found a "paper on CRPS induced by HPV in literature." Exhibit 5 at 153.

The "History of Present Illness" section from Mr. Stoev's first visit to the Florida Spine Institute on November 10, 2016 states: "PT RECENTLY HAD THE

HPV INJECTION 10/16 THAT CAUSED THE FLARE OF THE CRPS. HAS NOT BEEN CONTROLLED SINCE." Exhibit 11 at 6 (caps in original). The source of this statement is unclear. This was Mr. Stoev's initial evaluation with this provider, and "a summary of care was not provided" by other physicians. The rest of the History appears to be informed by statements from Mr. Stoev. It is therefore possible that Mr. Stoev and/or his parents reported this to the doctor, as they had done with Dr. Nickeson.

On June 2, 2017, Dr. Nickeson wrote:

> The parents raised concern today about whether HPV vaccine may have triggered his illness. They found some medical literature on a cluster of cases of complex regional pain syndrome related to HPV vaccination in Japan. Both parents are practicing physicians. I am not familiar with this connection and may have to look up any relevant literature in that area…Regarding relationship of his illness to HPV vaccine, I think without the need for scientific proof of connection to that product, he would likely qualify for consideration through the Federal Vaccine Compensation System. I will help the parents investigate this avenue which could help offset his significant medical care expenses.

Exhibit 5 at 217-18.

On October 6, 2017, Dr. Nickeson wrote: "I have seen the literature about connection of vaccine products with onset of complex regional pain syndrome and I think that this is something for the scientists to continue working on. However, based on current knowledge, I think that [Mr. Stoev] deserves consideration from the Federal Vaccine Injury Compensation Pool." Id.

Dr. Nickeson wrote a letter in support of this position, dated November 2, 2017:

> [Mr. Stoev's] parents called to my attention a series of research studies on low incidence serious adverse events associated with HPV vaccines. This family suspects their son's illness was precipitated by his receiving the HPV vaccine.
>
> Credible researchers in Japan, Sweden, Denmark, and other European centers are actively investigating CRPS in some patients as a vaccine-induced rare disorder. Though the science on this association of [Mr. Stoev's] disabling illness with his preceding use of HPV vaccine is not

> completely settled, logically he should be a candidate for compensation through the National Vaccine Injury Compensation Program.

Id. at 235; Exhibit 14.

b) Discussion

"[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect shows that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1326 (internal quotation marks omitted). However, opinions from treating physicians are not conclusive; "Any such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court." 42 U.S.C. § 300aa–13(b)(1).

"A variety of circumstances bear on a special master's decision with respect to treating physicians' opinions. Among the many circumstances that might be weighed: clarity and context of the treating physician's opinion; nature and duration of the physician's relationship with the vaccinee; the physician's specialty and level of expertise; and the consistency of the treating physician's opinion with the medical record." Isaac v. Sec'y of Health & Hum. Servs., No. 08-601V, 2012 WL 3609993, at *25 (Fed. Cl. Spec. Mstr. July 30, 2012), mot. for rev. denied, 108 Fed. Cl. 743 (2013), aff'd, 540 F. App'x 999 (Fed. Cir. 2013).

The value of opinions from Mr. Stoev's parents, who are medical doctors, is questionable. The Doctors Stoevs' statements that they suspected the HPV vaccine caused the flare-up very early on are supported by Dr. Nickeson's notes. See Exhibit 5 at 153 (noting the parents' concerns at the October 25, 2016 appointment). Although they are competent to treat him, they did not file any medical records regarding their treatment of Mr. Stoev before, during, or after the flare-up. The absence of records created by the Doctors Stoev does not prevent a finding that they sincerely believed the HPV vaccine caused a significant flare-up of Mr. Stoev's CRPS. The more significant issue concerns the basis for their belief. See Doyle v. Sec'y of Health & Hum. Servs., 92 Fed. Cl. 1, (2010) ("Merely conclusory opinions--or ones that are nearly so as unaccompanied by elaboration of critical premises—will not suffice as proof of causation, no matter how vaunted or sincere the offeror"). The sole basis they provide for "suspecting" the vaccine was that it was the only clinical thing that happened to Mr. Stoev around the time of his flare-up. This rationale is not persuasive in this case. See Fesanco v. Sec'y of Health & Hum. Servs., 99 Fed. Cl. 28, 34 (2011) (notation that provider was "suspicious" that injury may be related to vaccine was not an

affirmative medical opinion of causation); Orgel-Olson v. Sec'y of Health & Hum. Servs., No. 15-285V, 2022 WL 1598143, at *34 (Fed. Cl. Mar. 11, 2022) (little weight given to providers' "suspicion" of vaccine causation where "suspicion was based largely on temporality" and providers were equivocal.).

Dr. Nickeson's work, too, falls short. Dr. Nickeson did not consider the HPV vaccine as a possible cause for a worsening of Mr. Stoev's condition until the Stoevs raised the possibility. He stated that he was "not familiar" with the potential connection between the vaccine and CRPS but opined that "without the need for scientific proof of connection to that product," Mr. Stoev might qualify for compensation from the Program. Exhibit 5 at 217-18 (June 12, 2017). He later researched the topic but stated that "the science on this . . . is not completely settled." Exhibit 14 (November 2, 2017). Dr. Nickeson appears to stop short of stating that the HPV vaccine caused an adverse consequence to Mr. Stoev. Instead of indicating the HPV vaccine harmed Mr. Stoev, Dr. Nickeson wrote about Mr. Stoev's potential eligibility:

> [Mr. Stoev] should qualify for consideration through the Federal Vaccine Compensation System.
>
> [Mr. Stoev] deserves consideration from the Federal Vaccine Injury Compensation Pool.
>
> [L]ogically he should be a candidate for compensation through the National Vaccine Injury Compensation Program

Exhibit 5 at 217-28; 235; 238 (emphasis added).

Additionally, the Stoevs and Dr. Nickeson reviewed case series and case reports when researching whether the HPV vaccine could cause a flare-up of CRPS. As discussed above, this set of literature has been consistently discredited in the Vaccine Program. A shaky foundation may justify the rejection of a treating doctor's opinion. See Hazlehurst v. Sec'y of Health & Hum. Servs., 604 F.3d 1343, 1347, 1354 (Fed. Cir. 2010) (no error in special master's decision to discount opinion of a treating doctor who relied heavily upon unreliable studies).

Finally, nothing in the record indicates that Mr. Stoev's treating physicians conducted any analyses or tests to determine whether Mr. Stoev actually had an adverse reaction to the vaccine. In his expert report, Dr. Nickeson explains that "lab tests delving into autoimmunity . . . were not done as there was no medical indication for such tests." Exhibit 42 at 7. "These tests were not done as I was not researching pathogenesis of CRPS and did not have informed consent or an

approval protocol to obtain them." Id. The absence of these tests does not prevent Mr. Stoev from meeting his burden under Althen prong 2, but the medical records state no basis for his doctors' suspicion besides temporal proximity. See Zumwalt v. Sec'y of Health & Hum. Servs., 146 Fed. Cl. 525, 541 (2019) (no error if special master's finding that "a temporal relationship, alone, is not a sufficient basis upon which to find causation"); Veryzer v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 344, 355–56 (2011) (special master did not apply standard of medical certainty when noting the absence of test results during thorough review of all evidence), aff'd, 475 F. App'x 765 (Fed. Cir. 2012).

In sum, Mr. Stoev's treating physicians did not state a persuasive basis for their opinions that the HPV vaccine was in fact the trigger for his flare-up. "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Solak v. Sec'y of Health & Hum. Servs., No. 14-869V, 2020 WL 9173158, at *19 (Fed. Cl. Spec. Mstr. Feb. 19, 2020). While the views of Mr. Stoev's physicians have been considered, they do not by themselves satisfy the second Althen prong. See Isaac, No. 08-601V, 2012 WL 3609993, at *26 (giving little weight to physicians' notations where, "[in] contrast to cases in which the record reveals extensive analysis of the causation issue, it appears in this case that once the diagnosis of GBS was made there simply was very little medical attention paid by treating personnel to the cause of Petitioner's illness.").

3. Opinions Generated for the Purposes of Litigation

a) Summary of Opinions

Mr. Stoev submits the theory "that the HPV vaccine can trigger an immune-mediated autonomic dysfunction in certain instances," particularly in patients "who were already within a susceptible population at the time of administration." Exhibit 35 at 2 ¶ 4. Dr. S. Stoev stated that Mr. Stoev is one of these susceptible patients but did not elaborate. Id. at 2 ¶ 6. Dr. S. Stoev averred that: "None of the testing he has undergone has led to a different causative factor and there was nothing else that happened to him during the relevant time period that could explain such a rapid and extreme change in his condition." Id. at 6 ¶ 20.

In addition to discussing various articles, which were considered as part of the Althen prong one / Loving prong four aspect in Section IV.A, Dr. Nickeson discussed his treatment of Mr. Stoev before the vaccination. Exhibit 34 at 3-5 ¶¶ 8-18. Dr. Nickeson concluded Mr. Stoev's condition "was significantly aggravated after receiving the HPV vaccination." Id. at 5 ¶ 18. Dr. Nickeson

pointed out that "there is an absence of any other causal factors that I am aware of that would have caused such a rapid and dramatic decline in [Mr. Stoev's] condition during this time period other than the HPV vaccination." Id. at 9 ¶ 32.

Dr. Rose argued that a vaccine-caused flare-up would imply two distinct pathogenic triggers: a non-autoimmune mechanism for the initial onset and previous flare-ups, and an autoimmune mechanism in September 2016. Exhibit A at 21. He noted the clearly emotional triggers of two flare-ups (the passing of Mr. Stoev's grandmother and the family dog), and opined that the initial tripping incident was also of an emotional/psychological nature:

> The period of latency (3-4 days) (Ex 1) between the tripping event (trigger) on 3/13/2015 and the beginning of the CRPS as well as the delayed recognition of the trigger-documented by Dr Gekht five months later on [8/3/2015] (Ex 4 at 33) suggest that this trigger was not physical in the sense of tissue damage but emotional trauma (a stressful life events).

Id. at 18, 19. Dr. Rose further stated: "I have not seen any evidence in the literature of a viable model to support such dual claim at different stages of the same disease," and "The biological mechanism proposed (autoimmunity) would transgress basic rules of disease pathogenesis by invoking a different mechanism for disease onset and for exacerbation and doing so without any credible explanation." Id. at 21, 33.

Dr. Nickeson first questioned Dr. Rose's idea that the onset was triggered by an emotional/psychological event, as neither Mr. Stoev nor the medical records describe it as such. Exhibit 39 at 8. Dr. Nickeson also argued that there is no support for the view that CRPS must have a singular trigger, and mentioned that many chronic illnesses, such as asthma and chronic arthritis, are exacerbated by different subsequent external stimuli even when a virus or vaccine was not the original cause. Id. at 8-9.

Dr. Rose distinguished those examples from the case at hand: "the underlying claim here is beyond a simple multiplicity of triggers as in the examples but a claim that presupposes a separate pathogenic mechanism." Exhibit H at 9. "Neither the inflammation induced by viral infections in the respiratory tree for asthma nor the purported disease activation of the immune system by vaccinations requires an alternative underlying mechanism of either asthma or [juvenile idiopathic arthritis.]" Id. However, here, a vaccine-induced autoimmune mechanism would differ from the previous traumas and emotional stressors that

were at play until that point. Id. Dr. Rose observed that, if Mr. Stoev suffered from an autoantibody mediated case of CRPS from the onset, the autoantibodies would have been present 20 months prior to vaccination; however, as these antibodies were never tested, it is unknown whether they were present. Id. at 9, 12.

Dr. Nickeson responded that "In a single CRPS patient new stimuli can precipitate a flare in the condition." Exhibit 42 at 4. He argued that Dr. Rose conceded such when he listed the multiplicity of events associated with CRPS episodes, for example, onset being induced by minor trauma and later aggravation caused by a strong emotional event. Id.

The parties also discussed the nature of Mr. Stoev's aggravated symptoms. Dr. Nickeson stated that Mr. Stoev's symptoms after September 2016 "became more focused on strength issues in his lower extremities rather than the sensory and autonomic neuropathy" which was previously seen with Mr. Stoev's CRPS. Exhibit 39 at 2-3. Likewise, Mr. Stoev recognized "a change in the focus of his symptomology and treatment," with his primary symptoms initially being pain and allodynia but shifting to issues with strength, ambulation, and leg weakness after September 2016. Pet'r's Reply Br. at 9. However, as Dr. Rose explained: "By being associated with an agonist effect on receptors of the autonomic system one would expect their effect to be associated with more rather than less vasomotor (autonomic) elements in the clinical picture." Exhibit A at 22. Vasomotor symptoms would include temperature and skin color changes. Id. at 16 (Table: Budapest Criteria for CRPS). Mr. Stoev's experts did not respond to this point.

Dr. McGeady stated that Mr. Stoev's normal ESR and CRP levels weigh further against an inference of immune activation or injury. Exhibit C at 3 (citing Exhibit 29). Dr. McGeady also observed that Mr. Stoev did not respond to the steroid treatment, which "makes the immune mediated hypothesis less likely as well." Id.

Dr. Nickeson questioned the relevance of these points. Dr. Nickeson stated that CRPS is not believed to be an inflammatory disease, and systemic inflammation would cause elevation of ESR and CRP levels. Exhibit 39 at 11. As to the steroid treatment: "The fact of the matter is that sometimes steroids help CRPS patients and sometimes they don't. A CRPS patient's response to steroids is not indicative of pathogenesis." Exhibit 39 at 9.

Dr. McGeady explained that Mr. Stoev's theory of molecular mimicry between the HPV vaccine and elements of the central nervous system necessitates an immunopathologic process. As the "usual methods for detecting such

immunopathology were not employed in this case," Dr. McGeady looked for indirect evidence of a reaction, such as response to steroid treatment or evidence of acute inflammation. Exhibit I at 2. Dr. McGeady acknowledged that the absence of such indirect evidence is "not conclusive evidence against immunopathology, but it is the best that we have in this instance, and it points away from immunopathology." Id. In response, Dr. Nickeson argued that many children with immune-based chronic diseases, such as lupus, show normal acute phase reactants. Exhibit 42 at 6-7.

b) Discussion

Both Dr. Shoenfeld and Dr. Rose acknowledged that CRPS has an unknown etiology. Exhibit 40 at 4, Exhibit H at 10. Mr. Stoev and his experts presented evidence (Blaes, Kohr, Knudsen) suggesting an autoimmune pathogenesis of CRPS in at least a subset of CRPS patients. Pet'r's Br. at 30-31. The Secretary's experts do not question the assertion that some cases of CRPS may be autoimmune. However, the relevant question here is whether Mr. Stoev's CRPS is autoimmune.

A preponderance of the evidence supports a finding that Mr. Stoev's CRPS and specifically the aggravation in late 2016 is not autoimmune in nature. Although the onset of Mr. Stoev's CRPS was the result of the tripping incident in March 2015, later flare-ups stemmed from emotionally stressful events. While these are different triggers, they are all non-autoimmune mechanisms, as Dr. Rose points out. And, as Dr. McGeady highlighted, Mr. Stoev's normal ESR and CRP levels in March 2015 indicate that his CRPS is not autoimmune. Mr. Stoev and his experts have not persuasively explained how a different pathogenic mechanism – the HPV vaccine – could later come into play in the same disease course. However, even if a patient could have both autoimmune and non-autoimmune triggers in the course of their CRPS, Mr. Stoev's non-vasomotor symptoms after September 2016 do not support a finding of an autoimmune trigger. Additionally, Mr. Stoev did not respond to steroid treatment, indirectly indicating that his CRPS was non-autoimmune. In sum, the preponderance of the evidence does not support a finding of a logical sequence of cause-and-effect between Mr. Stoev's HPV vaccination and the flare-up.

C. Loving Prong 6 / Althen Prong 3

1. Law / Elements

The next element concerns the timing of the aggravation. The timing prong actually contains two parts. A petitioner must show the "timeframe for which it is medically acceptable to infer causation" and the "onset of" the disease occurred in this period. Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd without op., 503 F. App'x 952 (Fed. Cir. 2013). The anticipated interval largely derives from the offered theory. Langland v. Sec'y of Health & Hum. Servs., 109 Fed. Cl. 421, 443 (2013).

2. Arguments

Mr. Stoev and his parents recall that that a sudden and dramatic worsening of his condition began approximately three weeks after his HPV vaccination, on October 9, 2016. Exhibit 1 at 3; Exhibit 2 at 4; Exhibit 3 at 3; see also Pet'r's Br. at 8-9. The Stoev family and Dr. Nickeson emphasize that, in contrast to Mr. Stoev's condition prior to September 2016, he did not make significant improvements after this aggravation. Exhibit 1 at 3; Exhibit 2 at 4-5; Exhibit 3 at 4; Exhibit 34 at 4-5.

The Secretary and his experts argue that Mr. Stoev's medical records show that his flare-up began prior to the September 19, 2016 vaccination. Resp't's Br. at 38. Four days earlier, Dr. M. Stoev asked her assistant to call Dr. Nickeson's office "to request PT order as [Dr. Stoev] feels [Mr. Stoev] is starting to struggle again. [Mr. Stoev] missed school the other day and feels he would do better if he started PT again." Exhibit 5 at 156. Dr. Rose stated that the phone call posed a problem for attributing the pain to the HPV vaccine, as "the increase in pain was observed already **prior to vaccination**." Exhibit A at 21.

In an affidavit written three years later, Dr. M. Stoev explained that this request was based on her observations that Mr. Stoev "was still living a largely sedentary lifestyle at that point and [she] hoped that additional physical therapy would help him become more active and healthy." Exhibit 2 at 4. Dr. Nickeson argued that this explanation was corroborated by other contemporaneous medical records, as the records from the date of Mr. Stoev's vaccination note an absence of pain and discuss his lack of physical activity. Exhibit 39 at 5-6. Dr. Nickeson also argued that this flare-up was not part of a pattern of waxing and waning; although before there was some "variability in his condition, which is normal for CRPS

patients, there was never the type of extreme and rapid change in his condition he experienced after the vaccination." Exhibit 42 at 1. He disagreed with even classifying previous flare-ups as "episodes" given his view that there were not analogous to the flare-up at issue. Exhibit 39 at 2.

Dr. Rose stated: "Regardless of the fact that there may have been additional reasons for the request for an order of PT (obesity, lack of exercise) the statement suggest[ed] the *onset* of an exacerbation. And it is the time of onset what counts not the timing in which the apex of intensity of the flareup is reached when vaccine causation is in question." Exhibit H at 3. Neither Mr. Stoev nor his experts responded to these points. Dr. Rose also maintained that CRPS features a waxing and waning course, and argued that characterizing events as "episodes," "variability in condition," or "flare-up" is a distinction without a difference and of negligible relevance. Id. at 2.

3. Discussion

Dr. M. Stoev's affidavit does not fully account for the September 15, 2016 phone call. The statement that Mr. Stoev was "starting to struggle again" and that he missed school indicates that there was not only a concern that he was too sedentary, but that he was beginning to experience a reoccurrence of his symptoms.

The persuasive value of Dr. M. Stoev's explanation is undercut by the fact that it was made 3 years after the phone call. See, e.g., Vergara v. Sec'y of Health & Human Servs., 08-882V, 2014 WL 2795491, *4 (Fed. Cl. Spec. Mstr. May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded later in medical histories, affidavits, or trial testimony."). Additionally, the contemporaneous staff notes documenting the phone call are more reliable than the affidavit generated years later to submit with the petition. See, e.g., Zumwalt, 146 Fed. Cl. at 541 (no error in determination that witness testimony was less probative than contemporaneous notes where "causality views only came into focus…two and a half years after the first onset…and after this petition was filed."); Reusser v. Sec'y of Health & Human Servs., 28 Fed. Cl. 516, 523 (1993) ("[W]ritten documentation recorded by a disinterested person at or soon after the event at issue is generally more reliable than the recollection of a party to a lawsuit many years later.").

Regardless of these facts, the affidavit does not overcome the record's plain statement that, prior to the vaccine, Mr. Stoev was "starting to struggle again." See Milik v. Sec'y of Health & Hum. Servs., 822 F.3d 1367, 1380-81 (Fed. Cir. 2016)

(although special master characterized letter as "litigation driven," and "not contemporaneous to the events to which it [spoke]," special master did not reject letter for that reason, but reasonably found that petitioner's explanation did not make sense within the context of the original medical records.). A finding that a vaccinee's condition worsened before the vaccination means that the vaccination could not have caused the aggravation. See Locane v. Sec'y of Health & Hum. Servs., 685 F.3d 1375, 1381 (Fed. Cir. 2012).

V. Conclusion

Mr. Stoev and his family deserve respect for their strength and support as they have navigated this difficult disease course. However, the requirements of the Vaccine Program must be met before compensation can be awarded. Mr. Stoev has not established with preponderant evidence that an HPV vaccine can cause or aggravate CRPS, or that the HPV vaccine harmed him. Accordingly, he is not entitled to compensation.

The Clerk's Office is instructed to enter judgment in accordance with this decision unless a motion for review is filed. Information about filing a motion for review, including the deadline, can be found in the Vaccine Rules, available through the Court's website.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master

Appendix: List of Medical Articles Cited[1]

1. LJ Albert & RD Inman, Molecular mimicry and autoimmunity, 341 N. ENGL. J. MED. 2068 (1999); filed as Exhibit C-1.

2. Franz Blaes et al., Autoimmunity in Complex-Regional Pain Syndrome, 1107 ANN. NY ACAD. SCI. 168 (2007); filed as Exhibit 35-1.

3. Svetlana Blitshteyn et al., Autonomic dysfunction and HPV immunization: an overview, 66 IMMUNOL RES 744 (2018); filed as Exhibit 22.

4. Louise Brinth et al., Suspected Side effects to the quadrivalent human papilloma vaccine, 62 DAN. MED. J. 4 (2015); filed as Exhibit 20.

5. Rebecca E. Chandler et al., Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster Analysis of Reports in VigiBase, 40 DRUG SAF. 81 (2017); filed as Exhibit 17.

6. European Medicines Agency. HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS, London, United Kingdom (2015); filed as Exhibit A-10.

7. Akiyo Hineo et al., Autoantibodies against Autonomic Nerve Receptors in Adolescent Japanese Girls after Immunization with Human Papillomavirus Vaccine, 2 ANN. ARTHRITIS CLIN. RHEUMATOL. 1 (2019); filed as Exhibit 34-2.

8. Frank Huygen et al., Investigating Reports of Complex Regional Pain Syndrome: An Analysis of HPV-16/18-Adjuvanted Vaccine Post-Licensure Data, 2 EBIOMEDICINE 1114 (2015); filed as Exhibit A-8.

9. Anders Hviid et al., Association between quadrivalent human papillomavirus vaccination and selected syndromes with autonomic dysfunction in Danish females: population based, self-controlled, case series analysis, BMJ 2020;370:m2930; filed as Exhibit C-6.

10. Andreas Goebel et al., Passive transfer of fibromyalgia symptoms from patients to mice, 13 J. CLIN. INVEST. 13 (2021); filed as Exhibit 43-12.

[1] All articles have been considered.

11. Andreas Goebel & Franz Blaes, Complex regional pain syndrome, prototype of a novel kind of autoimmune disease, 12 AUTOIMMUN. REV. 682 (2013); filed as Exhibit 43-11.

12. Tian-Zhi Guo et al., Passive transfer autoimmunity in a mouse model of complex regional pain syndrome, 158 PAIN 2410 (2017); filed as Exhibit 43-14.

13. Darja Kanduc, Hydrophobicity and the Physico- Chemical Basis of Immunotolerance, 87 PATHOBIOLOGY 268 (2020); filed as Exhibit 40-6.

14. Darja Kanduc, Peptide cross-reactivity: the original sin of vaccines, 4 FRONT BIOSCI. 1393 (2012); filed as Exhibit 40-5.

15. Darja Kanduc, The role of proteomics in defining autoimmunity, 18 EXPERT REV. PROTEOMICS 177 (2021); filed as Exhibit 40-7.

16. Darja Kanduc et al., Massive peptide sharing between viral and human proteomes, 29 PEPTIDES 1755 (2008); filed as Exhibit C-4.

17. Tomomi Kinoshita et al., Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine, 53 INTERN. MED. 2185 (2014); filed as Exhibit 16.

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